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Synthesis of Difluoromethylated and Phosphorated Spiro[5.5]trienones via Dearomative Spirocyclization of Biaryl Ynones

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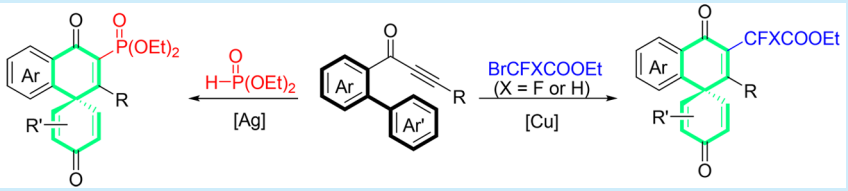
Supporting Information



ABSTRACT: Copper- or silver-catalyzed cascade radical addition/dearomative spirocyclization of biaryl ynones with fluoroalkyl bromides or diethylphosphite has been realized for the first time. This method provides a novel and step-economical protocol for the divergent synthesis of a wide range of difluoromethylated or monofluoromethylated and phosphorated spiro[5.5]trienones in moderate to high yields.

Spiro compounds exist in a large number of natural products, biologically active molecules, and functional materials.[1,2] In particular, spiro[5.5]trienones have been widely utilized as valuable intermediates for organic synthesis and drug discovery. Typical examples include platencin (Figure 1, **I**), a FabH and FabF dual inhibitor with potent broad-spectrum antibiotic activity, the natural product laurencenone B (Figure 1, **II**), and compound **III**, which is a spirane amine inhibitor against WT A/M2.[2e] As such, the exploration of novel and efficient strategies for the synthesis of spirocarbocycles continues to be an important task in organic synthesis.

In this aspect, spirocyclization via dearomatization has emerged as a very attractive strategy for the rapid synthesis of structurally diverse spiro molecules. Traditional methods for the synthesis of spiro compounds include oxidative dearomatization,[3] nucleophilic or electrophilic dearomatization,[4] and transition-metal-mediated dearomatization.[5] For example, the Pd-catalyzed intramolecular and intermolecular dearomatizing annulations of biaryl compounds were developed by the groups of Buchwald, Hamada, Luan and others (see Scheme 1A).[5b,d,i,j] Pioneered by Curran and co-workers, radical spirocyclization has become a highly efficient and alternative approach for constructing spiro carbo- or heterocycles, which permits the rapid construction of various spiro compounds from readily available starting materials. However, many methods have focused on the 5-exo-trig cyclization, thus leading to spiro[4.5]trienones or their analogues (Scheme 1B).[6] As compared to the 5-exo-trig cyclization, the 6-exo-trig cyclization

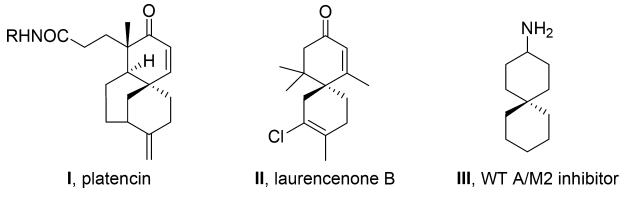


Figure 1. Significance of spiro[5.5]trienones.

Scheme 1. Dearomatizing Reactions for Access to Spirocycles

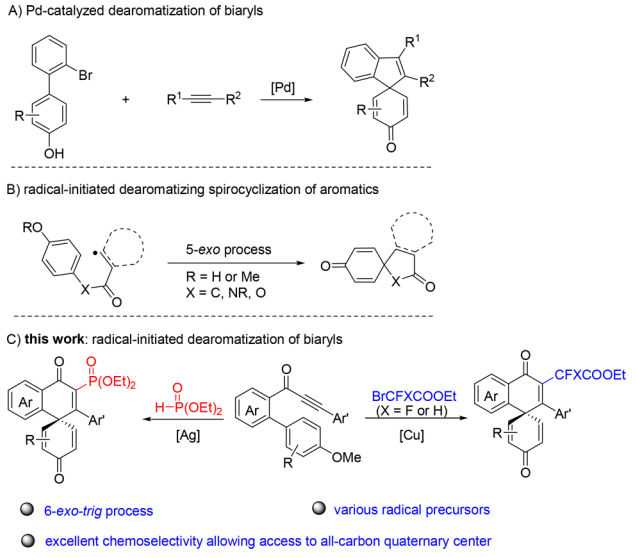


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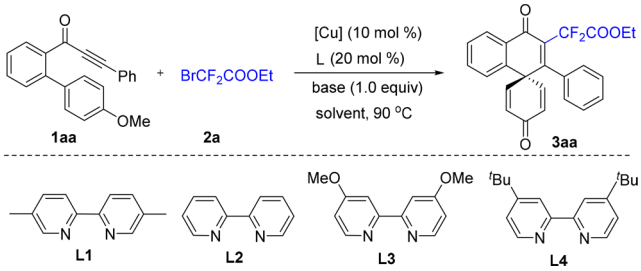
Table 1. Optimization of Reaction Conditions for Cu-Catalyzed Fluoroalkylation-Initiated Dearomative Spirocyclization[a]



entry	[Cu]	ligand	base	solvent	yield[b] (%)
1	CuCl	**L1**	K_2CO_3	MeCN	37
2	CuOAc	**L1**	K_2CO_3	MeCN	10
3	CuTc	**L1**	K_2CO_3	MeCN	trace
4	Cu_2O	**L1**	K_2CO_3	MeCN	56
5	Cu_2O	**L2**	K_2CO_3	MeCN	50
6	Cu_2O	**L3**	K_2CO_3	MeCN	66
7	Cu_2O	**L4**	K_2CO_3	MeCN	74
8	Cu_2O	**L4**		MeCN	37
9	Cu_2O		K_2CO_3	MeCN	trace
10	Cu_2O	**L4**	$KHCO_3$	MeCN	71
11	Cu_2O	**L4**	Na_2CO_3	MeCN	63
12	Cu_2O	**L4**	K_2CO_3	DMF	20
13	Cu_2O	**L4**	K_2CO_3	DCE	0
14	Cu_2O	**L4**	K_2CO_3	$PhCF_3$	0

[a]Reaction conditions: **1aa** (0.2 mmol), **2a** (0.4 mmol), [M] (10 mol %), **L** (20 mol %), base (0.2 mmol), solvent (2 mL), under N_2, 90 °C, 10 h. [b]Yields of isolated products. DCE = 1,2-dichloroethane.

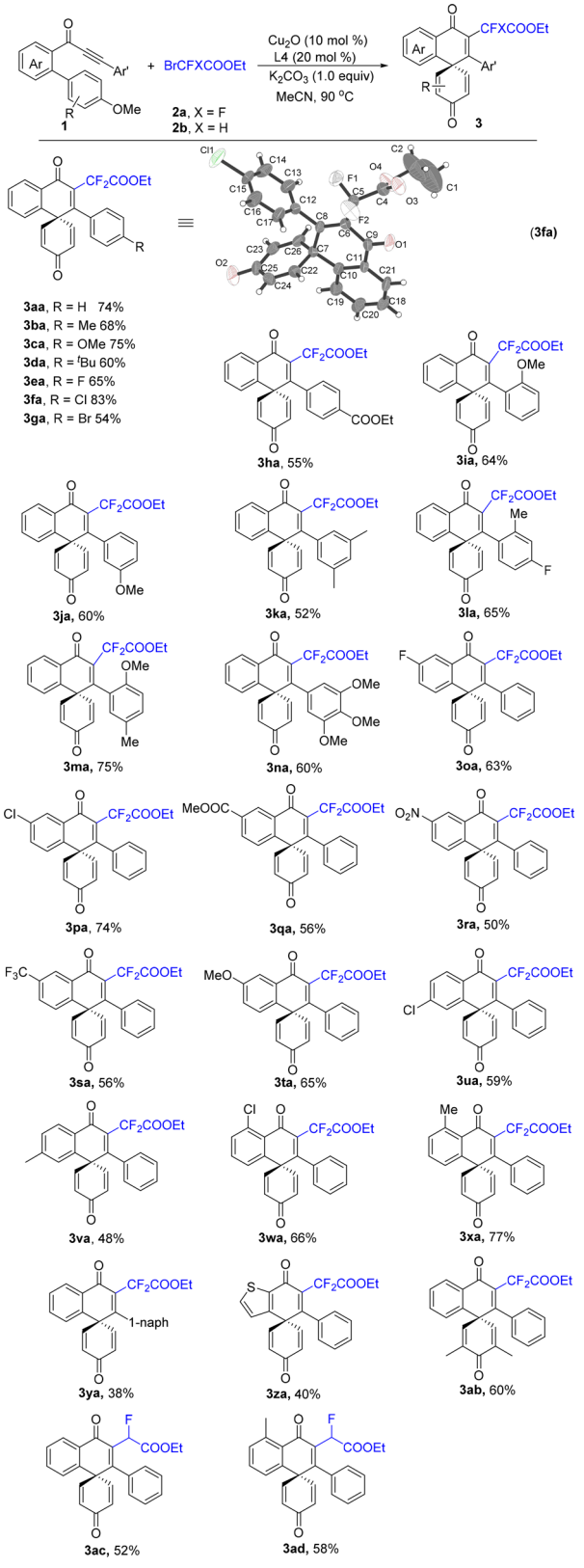
is more challenging,[7] and such a radical spirocyclization permitting the formation of spiro[5.5]trienones is highly desirable.[8]

On the other hand, biaryls are challenging substrates for the radical dearomatization, because of the challenge of controlling the site selectivity of radical cyclization. As part of our interest in radical reactions and fluorine chemistry,[9] we explored the possibility of radical addition/dearomatization of biaryl ynones to form the spiro[5.5]structural motif, which was reported to have special biological properties.[10] Here, we report a novel copper/silver-catalyzed cascade radical addition/dearomative spirocyclization of biaryl ynones with fluoroalkyl bromides or diethylphosphite as the radical source, producing difluoromethylated or monofluoromethylated and phosphorated spiro[5.5]trienones in good yields. The reaction constitutes a new advance in the uncommon 6-exo-trig radical dearomative spirocyclization process (see Scheme 1C).

Our initial study focused on the reaction of biaryl ynone **1aa** using $BrCF_2CO_2Et$ (**2a**) as the radical source. Selected results are shown in Table 1. The reaction proceeded in the presence of CuCl (10 mol %), **L1** (20 mol %) and K_2CO_3 (1.0 equiv) in MeCN at 90 °C, affording the spirocyclic product **3aa** in 37% yield (Table 1, entry 1). Encouraged by this preliminary observation, we attempted to improve the reaction efficiency by screening various copper salts and ligands (Table 1, entries 2–7).

It was found that Cu_2O was the best catalyst. Among the ligands screened, **L4** afforded the best yield (Table 1, entry 7). Low conversions were observed in the absence of the K_2CO_3 and ligand (Table 1, entries 8 and 9). The reaction was examined by using other bases such as $KHCO_3$ and Na_2CO_3 (Table 1, entries 10 and 11), but none of them could give comparable results. Finally, the effect of solvents was

Scheme 2. Scope of Fluoromethylated Spiro[5.5]trienones[a]



[a]Isolated yields are given. Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), Cu_2O (10 mol %), **L4** (0.04 mmol), base (0.2 mmol), solvent (2 mL), under N_2, 90 °C, 10 h.

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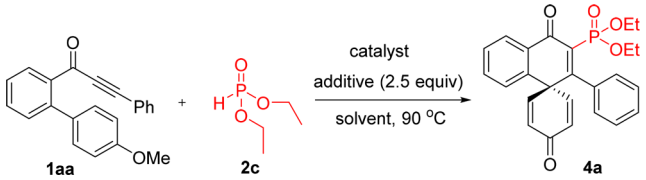
Table 2. Optimization of Reaction Conditions for Phosphorylation-Initiated Dearomative Spirocyclization[a]



entry	catalyst	additive	solvent	yield[b] (%)
1		$Mn(OAc)_3{\cdot}2H_2O$	AcOH	34
2[c]	$AgNO_3$		AcOH	46
3[c]	$AgNO_3$		MeCN	52
4[c]	AgOAc		MeCN	28
5[d]	$AgNO_3$	$Mg(NO_3)_2$	MeCN	44
6[d]	$AgNO_3$	$Zn(NO_3)_2$	MeCN	50
7[d]	$AgNO_3$	$K_2S_2O_8$	MeCN	62
8[d]	$AgNO_3$	$Na_2S_2O_8$	MeCN	30
9[d]	$AgNO_3$	$K_2S_2O_8$	MeCN/H_2O = 1:1	70
10[d]	$AgNO_3$	$K_2S_2O_8$	MeCN/H_2O = 1:2	50
11[d]	$AgNO_3$	$K_2S_2O_8$	MeCN/H_2O = 2:1	65
12[d]	$AgNO_3$	$K_2S_2O_8$	acetone/H_2O = 2:1	47

[a]Reaction conditions: **1aa** (0.2 mmol), **2c** (0.4 mmol), additives, solvent (2 mL) under N_2, 90 °C, 10 h. [b]Isolated yields. [c]AgX (2.0 equiv) was used. [d]$AgNO_3$ (20 mol %) was used.

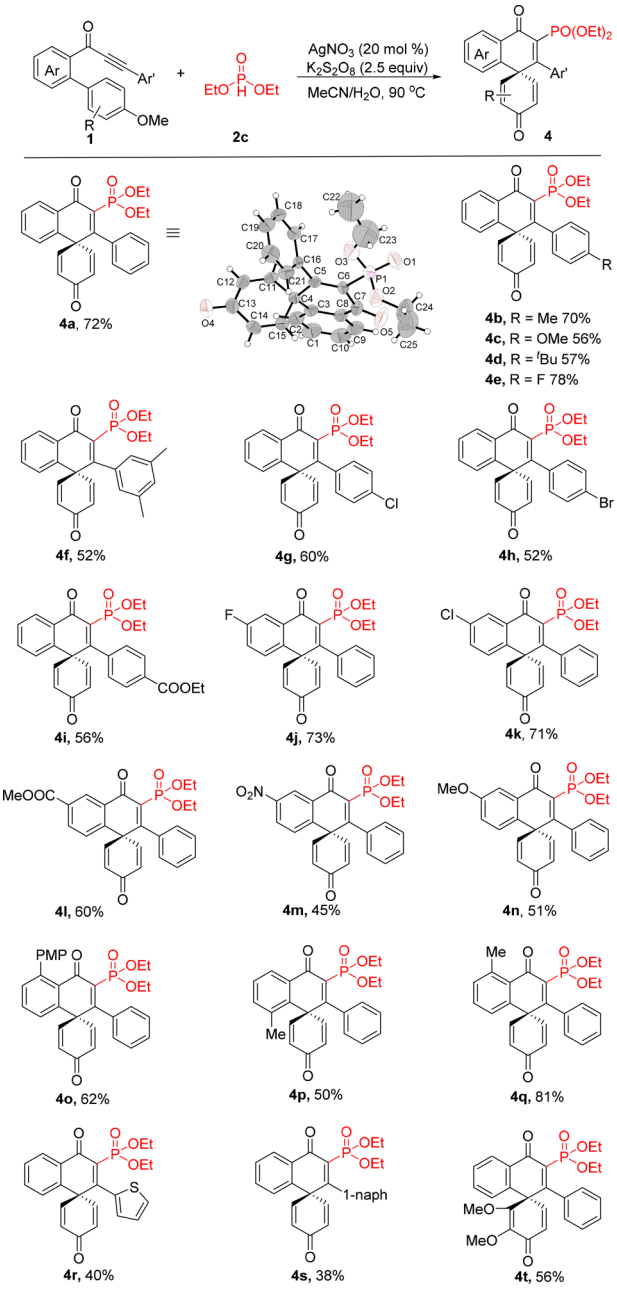
investigated. Employing common solvents such as DMF, DCE, and $PhCF_3$ dramatically reduced the yield (Table 1, entries 12–14) in the reaction.

To ascertain the scope and limitations of the reaction, many biaryl ynones **1** were investigated and the results are shown in Scheme 2. Generally, the electronic effect of substituents on Ar′ does not influence the reaction efficiency, and moderate to good yields of spiro[5.5]trienones were obtained (**3aa**–**3ea**). It is noteworthy that functional groups such as ether, ester, chloro, and bromo are compatible with the reaction (**3fa**–**3ja**), which offers an opportunity for further derivatization. The scope of Ar′ was also extended to polysubstituted substrates and biaryl ynones **1ka**–**1na** afforded the corresponding products in satisfactory yields (**3ka**–**3na**), indicating that the steric hindrance of Ar′ has little impact on the reaction.

After examining the effect of various substitutions on the Ar′ group, substitution on the Ar group in the reaction outline was investigated. Substrates bearing either electron-withdrawing or electron-donating groups affected the reactivity of **1**. In particular, substitution at the *ortho*-position of the benzoyl group had a positive effect on this transformation (**3wa**–**3xa**). Heteroaryl and naphthyl substituents were also compatible, and the expected products were found in relatively low yields (**3ya** and **3za**). The substrate with a Me group at the *ortho*-position of OMe (**1ab**) also formed the expected compound **3ab**. In addition, $BrCFHCO_2Et$ was attempted as the radical precursor, and the desired monofluoromethylated products were isolated in moderate yields (**3ac**–**3ad**). The structure of **3fa** was confirmed by X-ray crystallographic analysis.

To further expand this methodology, we next examined other radical precursors. Radical phosphorylation has become a highly efficient approach to synthesize phosphonates, which are widely utilized in organic synthesis.[11] Thus, phosphorylation-initiated dearomative spirocyclization of biaryl ynones was conducted using **1aa** and diethylphosphite (**2c**) as the model substrate (Table 2). When the reaction was run in a mixed solvent of

Scheme 3. Reaction Scope for the Synthesis of $PO(OEt)_2$-Containing Spiroconjugated Compounds[a]



[a]Isolated yields are given. Reaction conditions: **1** (0.2 mmol), **2c** (0.4 mmol), $AgNO_3$ (20 mol %), $K_2S_2O_8$ (0.5 mmol), MeCN (1 mL), H_2O (1 mL), under N_2, 90 °C, 10 h.

MeCN and H_2O (v/v = 1:1) at 90 °C for 10 h with $AgNO_3$ (20 mol %) as the catalyst and $K_2S_2O_8$ (2.5 equiv) as the oxidant, 70% yield of **4a** was isolated (see Table 2, entry 9).

We briefly examined the scope of this silver-catalyzed phosphorylation initiated dearomatization of biaryl ynones. The diversity of this transformation turned out to be satisfactory (see Scheme 3). Generally, the electronic properties of Ar and Ar′ in substrates **1** did not have distinct influence on the efficiency of the phosphorylation, and moderate to good yields of the spiro[5.5]trienones **4** were obtained. However, decreased yields were observed when the Ar′ is a heteroaryl, such as the thiophenyl group (**4r**). The structure of **4a** was

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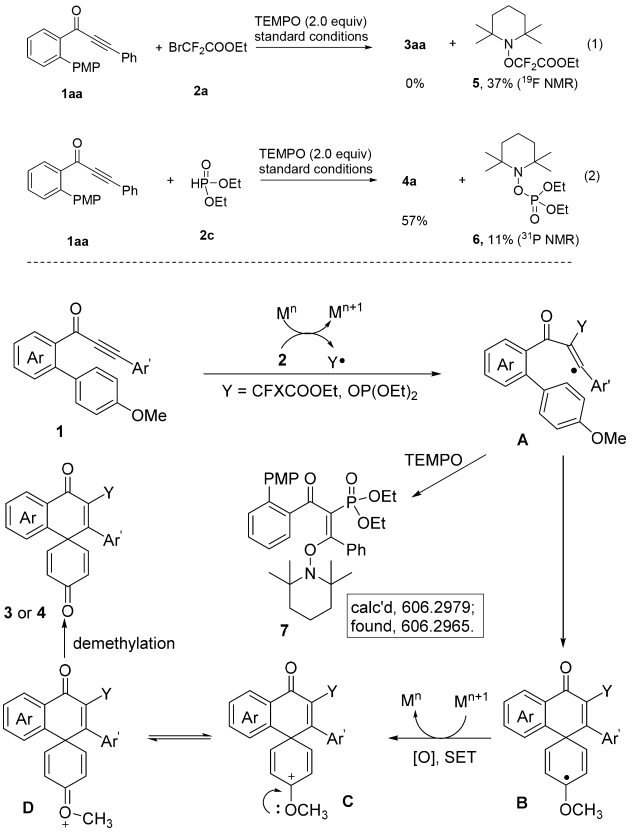
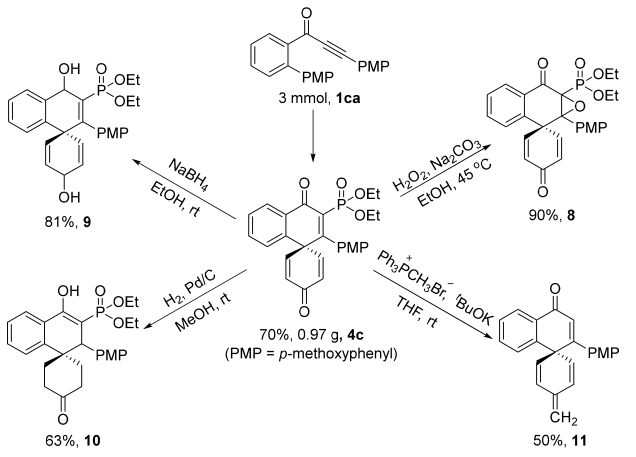
Scheme 4. Proposed Mechanism



Scheme 5. Gram-Scale Preparation of 4c and Its Derivatization



determined by X-ray crystallographic analysis. It is worth mentioning that the sterically demanding substrate **1af** produced the desired product **4t** in 56% yield.

In order to probe the mechanism, the reaction between **1aa** and **2a** or **2c** was conducted in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). The reactions were completely or partially inhibited and the TEMPO-adducts were detected by ^{19}F and ^{31}P NMR analysis, respectively (Scheme 4, eqs 1 and 2).[12,13] Based on these results and previous reports,[6a,14] a proposed pathway for the formation of spiro[5.5]trienones is depicted in Scheme 4. Initially, radicals $Y^{\bullet}$ are generated in situ from **2** in the presence of copper or silver catalyst. Radical addition of $Y^{\bullet}$ to C−C triple bonds of **1** affords a vinyl radical **A**, which undergoes 6-*exo*-trig cyclization to form the radical **B**. Intermediate **B** is then oxidized by M^{n+1} to form oxocarbenium ion **D**. Finally, the corresponding products **3** or **4** are formed after demethylation. The observation of a TEMPO-adduct **7** by HRMS suggests the formation of intermediate **A**, thus supporting the proposed mechanism.

The scalability of this method was also investigated, and a 3 mmol scale reaction yielded 0.97 g of product **4c** (70% yield) from **1ca**. With **4c** in hand, further functionalization was performed (see Scheme 5). The biologically relevant epoxyquinone structure **8** could be obtained in excellent yield via oxidation, while reduction of the ketone or the olefin furnished alcohol or ketone (**9** and **10**, respectively) in good yield. Interestingly, we found that the phosphoryl group could be removed under the Wittig reaction conditions, and compound **11** could be prepared.

In summary, we have successfully developed a novel copper/silver-catalyzed cascade radical addition/dearomative spirocyclization of biaryl ynones with fluoroalkyl bromides or diethylphosphite as the radical source. The reaction provides a divergent and efficient access to difluoromethylated, monofluoromethylated and phosphorated spiro[5.5]trienones under mild reaction conditions. It represents one of the 6-*exo*-trig radical dearomative spirocyclization process and should be useful for the construction of spiro compounds. Further application of the protocol in the preparation of a variety of novel and potentially useful polycyclic compounds, as well as natural products, is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01027.

Detailed experimental procedures, characterization data for all new compounds **3** and **4** (PDF)

Accession Codes

CCDC 1542882−1542883 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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